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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/282,879	03/31/99	CHATTERJEE S	46906-2-DIV

HM12/0125

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1652	5

DATE MAILED: 01/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/282,879	Chatterjee et al.
Examiner	**Group Art Unit**
Manjunath N. Rao	1652

☒ Responsive to communication(s) filed on *Nov 9, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *13-30* is/are pending in the applicat

Of the above, claim(s) *18-30* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *13-17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Claims 13-30 are still at issue and are present for examination.

Applicant's election with traverse of Group I, Claims 13-17 in Paper No. 4 is acknowledged. The traversal is on the ground(s) that the search and coexamination of Groups II and V would not be a burden to the Examiner as they have overlapping classification. This is not found persuasive because while the searches for the three groups overlap, they are not coextensive. The search for Groups II and V would each require the search of subclasses unnecessary for the search of elected Group I. For example, search of Group I would require search of subclass 435/18 and search of Group V would require search of subclass 435/2 in addition to different non-patent literature search. Furthermore, the above groups are clearly drawn to different inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18-30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 4.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13-14 appear to be incomplete. Claims 13-14 are drawn to a method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder comprising contacting the agent with the neutral sphingomyelinase. However, mere contacting a test compound with a sphingomyelinase will not identify the compound as one that modulates the activity of the enzyme, unless such activity is compared with the activity of the enzyme in the absence of that compound. Amending the claims to include the phrase "in the presence and absence of the test compound" or the like would overcome this rejection.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder comprising contacting a candidate pharmacological agent with native human sphingomyelinase, does not reasonably provide enablement for an identical method of identifying a compound comprising the use of any fragment or any derivative of human neutral sphingomyelinase. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 13 and 15 are so broad as to encompass use of any fragment of human sphingomyelinase or a derivative (mutant or a variant) of human sphingomyelinase wherein one or more amino acids have been replaced in the amino acid sequence of human neutral sphingomyelinase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of sphingomyelinases and its fragments broadly encompassed by the methods of the claims.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method comprising using wild type human neutral sphingomyelinase.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art

would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims drawn to a method which encompass methods of use of all modifications and fragments of human neutral sphingomyelinase because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting enzyme activity; (B) the general tolerance of sphingomyelinases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including uses of sphingomyelinases with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a sphingomyelinase having the desired biological characteristics for the above method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

5. Claims 13 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 13 and 15-17 are directed to a method comprising the use of a genus of polypeptides which encompass fragments or derivatives (mutants in which one or more amino acids are substituted) of native human sphingomyelinase.

The specification defines "fragments and derivatives" of sphingomyelinase (see page 8-9) as proteins or polypeptides which retain essentially the same or 50%, 75%, or 95% of the biological function or activity as the protein with SEQ ID NO:2 or in which one or more amino acids of SEQ ID NO:2 have been substituted with a conserved amino acid or a peptide in which one or more amino acid residues includes a substituent group etc. This definition does not provide any specific information about the structure of all mutants of SEQ ID NO:2 (i.e. where are the regions within which mutations are likely to occur) nor discloses any function for all mutations. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO:2 relates to the structure of any known mutant. The general knowledge in the art concerning mutants and derivatives dose not provide any indication of how a single amino acid sequence is representative of unknown amino acid sequences. The genus of peptides, polypeptides that comprise the claimed fragments and derivatives of human sphingomyelinase in the above method is a large variable genus. Therefore, many functionally and structurally unrelated polypeptides and proteins are encompassed within

the scope of these claims. The specification discloses only a single species of the claimed genus (i.e the sequence SEQ ID NO:2) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chatterjee et al. (J. Biol. Chem., 1989, Vol. 264(21):12554-12561) and Ogita et al. (WO 9518119, 7-6-1995) in view of the high level of knowledge in the art. Claims 13-17 in this instant application are drawn to a method of identifying a compound which when used in a reaction comprising sphingomyelin as the substrate, the neutral sphingomyelinase as the enzyme and ceramide as the cleaved product, leads to reduced concentration of the cleavage product such that the identified

compound could be used in the diagnosis or treatment of human neutral sphingomyelinase related disorder.

Chatterjee et al. teach an assay method for the activity of neutral sphingomyelinase wherein a mixture of sphingomyelinase and the substrate sphingomyelin is first formed and the mixture is treated under conditions wherein the substrate is cleaved and cleaved product is detected (see page 12555, 2nd column). Chatterjee et al. also teach that sphingomyelinase catalyzes the hydrolysis of sphingomyelin to ceramide and phosphorylcholine at both acidic and neutral pH. The reference also teaches that the study of neutral sphingomyelinases are necessary in view of its involvement in gentamicin-mediated nephrotoxicity in man and also due to the involvement of sphingosine, released as a consequence of the action of sphingomyelinase, in a cascade of reactions leading to the regulation of protein kinase C activity (see page 12554, Introduction). Thus it appears that the substrate, cleavage product and the importance of the whole sphingomyelinase reaction was common knowledge in the art. However, the above reference does not teach the above described assay for the detection of a pharmacological agent.

Ogita et al. teach the manufacture of a sphingomyelinase inhibitor obtained from a microorganism and its use to treat a variety of diseases and disorders such as HIV, diabetes, leukemia, cachexia etc.

With the high level of knowledge existing in the art of enzymology and the importance of sphingomyelinase inhibitors taught in the above references, particularly Ogita et al. it would have been obvious to one skilled in the art at the time the invention was made to use the assay

Chatterjee et al. to develop a method of identifying other compounds which inhibit sphingomyelinase and thus would be expected to be useful in diagnosis or treatment of a human neutral sphingomyelinase related disorder. Chatterjee et al. teach that one would be motivated to do this in order to study the biochemical mechanisms involved in gentamicin-mediated nephrotoxicity or in Niemann-Pick disease. One would have a reasonable expectation of success since Chatterjee et al. provide a robust and time tested assay method and Ogita et al. demonstrate the existence of a chemical compound which inhibits sphingomyelinase.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 6:30 a.m. to 3:00 p.m. If attempts to reach the Examiner

by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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Manjunath N. Rao

January 24, 2001